II. Remarks

A. Amendments to the Claims and Formal Matters

Claims 62, 66-71 and 75-82 and 87-93 are pending in this application. Claims 87 and 90-92 have been withdrawn by the Examiner. Claims 62, 67, 68, 70, 71, 76, 77, 81 and 82 are proposed herein to be amended. Claims 66, 69 and 75 are canceled with this amendment. Upon entry of these amendments, claims 62, 67, 68, 70, 71, 76-82 and 87-93 will be pending with claims 62, 67, 68, 70, 71, 76-82, 88, 89 and 93 under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

Claim 62 is amended to recite a "fusion protein of IFNAR2 comprising (1) the sequence of SEQ ID NO:2 and (2) a human immunoglobulin constant domain." Claim 62 is also amended to recite that the affinity of the fusion protein for IFN-β is synergistically increased "at least 25 to 100-fold" compared to wild type human IFNAR2. Support for the amendments may be found throughout the specification as filed with exemplary support at page 6, lines 7-14 and 18, lines 16-20.

Claim 68 is amended to recite that the affinity of the fusion protein for IFN-β is "at least 50-fold" higher than wild type polypeptide. Support for this amendment is found in the specification as filed at least at page 6, lines 7-14.

Claims 67, 70, 71, 76, 77, 81 and 82 are amended to correct dependency.

Applicant respectfully submits that no new matter has been added by the amendment.

B. Patentability Rejections

1. The Rejections Under 35 U.S.C. §112, First Paragraph – Enablement – Should be Withdrawn

a. Claims 62, 66-71, 75-82 and 93

Claims 62, 66-71 and 75-82 and 93 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking an enablement for the full scope of the invention.

Applicants herein amend claim 62 to recite a fusion protein comprising (1) the sequence of SEQ ID NO:2 and (2) a human immunoglobulin constant domain which exhibits wherein the affinity of said fusion protein for IFN-β is synergistically increased at least 25 to 100-fold compared to wild type human IFNAR2. Applicants believe that these amendments overcome the Examiner's rejections.

One of ordinary skill in the art would, in view of the disclosure provided by the instant Application, and of common general knowledge at the time the present Application was filed, make the claimed fusion proteins and identify those polypeptides which exhibit the claimed synergistically enhanced affinity for IFN-β without recourse to undo experimentation. Accordingly, Applicants respectfully submit that the full scope of the rejected claims is enabled by the present disclosure and request that the Examiner withdraw the rejection for lack of enablement.

b. Claims 88 and 89

Claims 88 and 89 stand rejected under 35 U.S.C. §112 for an alleged lack of enablement for the reasons of record. Applicant respectfully traverses.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In determining whether a disclosure satisfies the enablement requirement (and whether any necessary experimentation is "undue") the Examiner should consider the *Wands* factors. It is improper for the Examiner to conclude that a disclosure is not enabling based on analysis of only one of the *Wands* factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands*, 858 F.2d at 737, 740. A determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the factual considerations set forth by the Federal Circuit in *In re Wands*. *See also* MPEP 2164.01(a).

i. The Level of Skill in the Art is High

The relative skill of those in chemical and biological arts is high. Methods of making the claimed fusion proteins were known in the art and the experimentation involved to use the claimed fusion proteins in accordance with the full scope of claims 88 and 89 would have been well within the skill of those in the art and therefore would have been routine.

ii. The State of the Art

The activity of type I interferons in modulating the immune system was known and it was known that type I interferons act through a cell surface receptor complex to induce such a biological effect. See specification, pages 1-2, paragraphs [0005]-[0006].

European Patent No. EP1037658B, at Example 11, proves that injection of mice with IFN-β complexed to soluble wild type IFNAR2 enhances the serum half life of IFN-β. Importantly, similar enhancement of the serum half life of IFN-β was observed following an injection of IFN-β followed by a second, separate injection of soluble wild type IFNAR2 (sIFNAR2). Thus, EP1037658 demonstrates the ability of administered sIFNAR2 to complex *in vivo* with circulating IFN-β. Moreover, such enhanced half life is demonstrated to result in enhancement and prolongation of IFN-mediated efficacy *in vivo* and such activity would be useful in any disease, such as multiple sclerosis, in which IFN-β itself is active. *See* EP1037658 at Example 14. Importantly, intrathecal administration of the type I interferon IFN-β has been demonstrated to reduce the exacerbations of multiple sclerosis. *See* specification, page 4, paragraph [0010].

iii. The Presence or Absence of Working Examples

The present disclosure, at Examples 4 and 7 and Figure 4, provides working examples demonstrating enhanced activity of IFN-β/IFNAR2 (wild type and mutant) complexes relative to free IFN-β. In the experiments, the addition of IFNAR2 to a constant amount of IFN-β resulted in a dose-dependent increase in cell survival upon challenge with vesicular stomatitis virus (VSV). As cell survival is dependent on IFN-β activity, such a result demonstrates that addition of IFNAR2 stabilizes and enhances the activity of IFN-β. Importantly, for its use as a carrier of IFN-β, a significantly lower concentration of the claimed polypeptides is required relative to the wild type sIFNAR2

due to the synergistic increase in affinity for IFN-β resulting from the claimed mutations. As shown by EP1037658, these *in vitro* results correlate with an enhancement and prolongation of IFN-mediated efficacy *in vivo* and are applicable to any therapeutic indication in which free IFN-β has shown therapeutic activity, such as multiple sclerosis.[1]

iv. The Evidence, When Properly Considered in its Entirety, Compels a Finding that the Full Scope of Claims 88 and 89 are Enabled.

Applicants respectfully submit that the instant disclosure, along with knowledge in the art at the time of filing, provides the guidance necessary to enable the full scope of claims 88 and 89 in view of at least (1) the working examples of the instant specification demonstrating that the claimed fusion proteins are superior carrier molecules for IFN-β and enhance the activity of IFN-β *in vitro*; (2) the state of the art which demonstrates that wild type sIFNAR2 acts as a carrier molecule for IFN-β *in vivo* following its injection resulting in prolonged and enhanced IFN-β activity; and (3) the high level of skill in the art allowing the routine determination of adjustments and manipulations of the disclosed optimal range of claimed fusion protein (0.24 nM – 0.4 nM) to achieve the claimed methods.

[1] In fact, the same ratio as used to maximize the generation of active complex *in vitro* resulted in elongated pharmacokinetics of IFN-β *in vivo*. *See* EP1037658 at page 13, lines 7-9 (citation is made with reference to WO 99/32141, an equivalent document).

2. The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

a. Claims 62, 66-71 and 75-76

Claims 62, 66-71 and 75-76 stand rejected under 35 U.S.C. §103(a) over Piehler *et al.* ("Piehler"). Applicants have amended claim 62 to recite the amount of increase in IFN-β binding – specifically, that the affinity of the claimed fusion protein for IFN-β is synergistically increased "at least 25 to 100-fold" compared to wild type human IFNAR2. Such an increase in affinity is neither taught nor suggested by Piehler et al.

The Examiner reads Piehler, first column, p. 232, as disclosing the presence of cooperative effects. However, the Examiner has once again isolated a statement in Piehler from its proper context. The statement in Piehler cited by the Examiner simply reflects the unsurprising notion that cooperative effects could potentially occur between point mutations. This statement is not specifically directed toward the instantly claimed mutations, nor does it constitute evidence that cooperative effects are expected. In fact, Piehler goes on to say that "[h]owever, the sum of interaction energies for individual mutations gives an estimation as to what extent the binding site is mapped by the residues investigated." Moreover, the authors note that "[f]or IFNa2, the sum of the interaction energies of all residues investigated is approximately 53 kJ/mol, which is close to the free energy of the complex formation." Accordingly, if anything, Piehler actually indicates that the sum of interaction energies for individual mutations (i.e., ignoring potential cooperative effects) provides a very good estimate of the interaction energy when such mutations are combined.

According to MPEP § 716.02(a), a demonstration of synergy is sufficient to overcome a *prima facie* case of obviousness where the results obtained are greater than those which could have been expected from the prior art to an unobvious extent and the results are of significant, practical advantage. As amended herein, the pending claims require that the affinity for IFN-β is increased at least 25 to 100-fold. Even if Piehler can be read to disclose the possibility of some cooperative effects, which is not admitted, an increase of at least 25 to 100-fold in affinity constitutes results greater than those which could have been expected from Piehler. In light of the unexpected, claimed synergistic increase, no indication of which is disclosed by Piehler and which could not have been

obvious to the ordinary artisan, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

b. Claims 77-82

At page 9 of the Final Office Action, the Examiner maintains his rejection of claims 77-81 under 35 U.S.C. §103(a) over Piehler and Campbell *et al.* ("Campbell") and applied this rejection to claim 82 as well. As discussed above, Piehler fails to teach or suggest the synergistic effect of the claimed double mutant H78A/N100A. Campbell, characterized by the Examiner as describing fusion protein constructs containing the hGH signal peptide in place of the native signal sequence of proteins, does nothing to remedy the defect of Piehler. Accordingly, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

C. Conclusion

In view of the above amendments and remarks, Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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